REMARKS

1. Claim Amendments

Claim 8 has been amended to recite a pharmacological composition for treating "a tumor cell that expresses L1CAM." The amendment is supported in the specification, for example, in paragraphs [0048] and [0050] and example 1, which all recite the use of anti-L1CAM antibody or L1CAM-binding fragment thereof in treatment of tumors that express L1CAM on their cell surface.

Amended claim 8 further recites an antibody which is not conjugated to a radionucleotide or toxin. The amendment is supported in the specification, for example, in paragraphs [0008], [0010], [0011] and [0012] and example 1, where the inventors disclose that, unlike as taught by the prior art, the L1CAM antibodies used in Applicants' invention were unconjugated antibodies and were, for the first time, shown to cause growth arrest in a cancer cell line when used in the unconjugated state.

No new matter has been added as a result of this amendment.

2. Claim Rejections under 35 USC §102(b)

Claims 8 and 9 are rejected under 35 US § 102(b) as being anticipated in view of Hoefnagel et al. Applicants traverse this rejection.

> According to M.P.E.P. §2131, *"[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

As discussed above, Claim 8 has been amended to recite a pharmaceutical composition for treating "tumor cells that express L1CAM" which further comprises unconjugated L1CAM antibodies or fragments thereof that are "not conjugated to a radioisotope or toxin". Hoefnagel, on the other hand, discloses therapeutic use [^{131}I]-labeled chimeric murine anti-human L1CAM mAb (chCE7) in nude mice bearing neuroblastoma xenografts. These teachings are acknowledged in the Office Action. Thus, the Action recognizes that Hoefnagel does not teach or suggest the use of an unconjugated anti-L1CAM antibody or L1CAM-binding fragment thereof. Indeed, there was as yet no evidence that L1CAM plays any role in cell proliferation at the time of filing of application (see specification, paragraph [0008]); Hofnagel taught the use of an anti-L1CAM antibody merely as a target for delivering the cytotoxic radioisotope to cells expressing L1CAM. Applicants for the first time, in co-owned and co-pending U.S. patent application Serial No. 10/199,820, filed July 17,

2002, now allowed), showed that L1CAM-derived genetic suppressor elements (GSEs) induce growth arrest in the majority and mitotic catastrophe in a minority of L1CAM-expressing cells (*see* specification, paragraph [0011]). This evidence established the unknown and unexpected role played by L1CAM in cell proliferation. Hence, as recited in Applicants' instant specification in paragraph [0012], "despite the evidence from GSE studies that inhibition of L1CAM protein expression is detrimental to tumor cell growth, there is no suggestion in the prior art that unconjugated antibodies that interact with L1CAM on cell surface may be of use in treatment of cancer." All references in the art thus far, including Hoefnagel, taught the use of antibodies having their cytotoxic effect due to the presence of conjugated radionuclide (as in the case of Hoefnagel) or a toxin. As is clearly stated in Hoefnagel, mAb chCE7 (which targets L1CAM protein) is used as a targeting vehicle for cell-specific radiation therapy (*see* page 366, last paragraph to page 367, first paragraph). Hence, Hoefnagel does not expressly or inherently disclose the use of unconjugated L1CAM antibodies or fragments thereof for treatment of cancer based on their anti-proliferative effect on cancer cells.

Consequently, Hoefnagel *et al.* does not teach all the limitations of Applicants' amended claims, and hence cannot anticipate claim 8 or its dependent claim 9. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 8 and 9 are rejected under 35 US § 102(b) as being anticipated in view of Carrel *et al.* Applicants traverse this rejection.

Like the teachings of the Hoefnagel reference discussed above, Carrel teaches the use of an [^{131}I]-conjugated L1CAM-binding fragment for targeting neuroblastoma tumor cells. As discussed above, Claim 8 has been amended to recite that the claimed pharmaceutical composition is for treating "tumor cells that express L1CAM" and comprises unconjugated L1CAM antibodies or fragments thereof which are "not conjugated to a radioisotope or toxin". Carrel neither teaches, suggests nor motivates the use an *unconjugated* anti-L1CAM antibody or L1CAM-binding fragment for treating L1CAM-expressing cancer. Thus, Carrel does not anticipate claim 8 or its dependent claim 9.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 8 and 9 are rejected under 35 US §102(b) as being anticipated in view of Mujoo *et al.* as evidenced by Wolff *et al.* Applicants traverse this rejection.

Mujoo teaches an L1CAM antibody that specifically recognizes and targets neuroblastoma cells. The results shown in the reference can in turn be used to demonstrate the usefulness of

conjugating L1CAM antibodies to drugs or radionuclides for treating neuroblastoma. Mujoo does not teach the use of unconjugated L1CAM antibodies or fragments thereof to treat cancers. Wolff *et al.*, as pointed out in the Action, merely discloses that the Mujoo antibody can bind human and murine L1 antigens. Since neither one of these references teaches or suggests that an unconjugated anti-L1CAM antibody or L1CAM-binding fragment can be used to treat cancers expressing L1CAM, these references cannot anticipate amended claims 8 and 9. (In view of this argument, Applicants do not reach the propriety *vel non* of citing two references in a rejection under 35 U.S.C. §102(b).)

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 8 and 9 are rejected under 35 US §102(b) as being anticipated in view of Patel *et al.* The Applicants traverse this rejection.

The Action points out that Patel teaches L1CAM antibodies that bind to human L1CAM antigen on neuroblastoma lines and rhabdomyosarcoma cell line JR1, and suggest the use of the antibodies for studying the molecular biology of L1CAM (see page 489). Patel does not teach or suggest the use of an unconjugated anti-L1CAM antibody or L1CAM-binding fragment for inhibition of tumor cell growth or treatment of cancer.

Consequently, Patel does not teach all the limitation of the claimed invention, and hence cannot anticipate the instant claims. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

4. Claim Rejections 35 USC §103(a)

Claim 8 is rejected under 35 USC §103(a) as being obvious over Rathjen *et al.* in view of Cleland *et al.* Applicants traverse this rejection.

In order to establish a *prima facie* case of obviousness the Patent Office must establish: 1) a teaching, suggestion or motivation found within the prior art or within the knowledge of one of skill in the art to combine or modify the references; and 2) a reasonable expectation of success in arriving at the claimed invention if the references are combined. The prior art references (alone or in combination) must teach or suggest *all* the claim limitations. MPEP § 706.02(j).

The combination of Rathjen *et al.* and Cleland *et al.* does not teach or suggest at least the following limitations of amended claim 8:

> "A pharmaceutical composition for the treatment of a cancer cell that expresses L1CAM ……. wherein the antibody is unconjugated to a radionucleotide or toxin."

Rathjen teaches L1CAM polyclonal and monoclonal antibodies that can react with neuroblastoma cells, and L1CAM polyclonal antibody fragments that can inhibit aggregation of neuroblastoma cells. The only process that the cited reference teaches where L1CAM protein is involved is cell adhesion (such as on page 7, right column, paragraph 2). Rathjen does not teach that L1CAM plays a role in cell proliferation. Applicants teach precisely that, in showing that L1CAM is involved in cell proliferation, wherein the inhibition thereof prevents proliferation. Furthermore, Rathjen does not teach, suggest, or motivate the skilled worker to use an unconjugated anti-L1CAM antibody or L1CAM-binding fragment for the treatment of cancer. Cleland does not cure this deficiency, because it also does not teach use of an unconjugated anti-L1CAM antibody or L1CAM-binding fragment for the treatment of cancer. Specifically, Cleland merely teaches excipients for stabilizing a monoclonal HER2 antibody.

Consequently, Applicants respectfully submit that the combination of Rathjen and Cleland do not render the instant claim obvious, because the cited references do not teach or suggest pharmaceutical compositions for the treatment of L1CAM expressing cancer by unconjugated L1CAM antibody or a fragment thereof.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 8 and 9 are rejected under 35 USC §103(a) as being obvious over Wolff *et al.* in view of Cleland *et al.* Applicants traverse this rejection.

Wolff teaches the use of 5G3 antibody to isolate and characterize L1CAM (or 5G3) glycoprotein from normal adult human brain, which was considered to be homologue of mouse L1CAM. The only mechanism that Wolff teaches is "the potential involvement of 5G3 or L1CAM in various human neurological disorders." (page 11946, last paragraph). Wolff does not teach, suggest, or motivate the skilled worker to use an unconjugated anti-L1CAM antibody or L1CAM-binding fragment for treatment of L1CAM-expressing cancers. Cleland, as discussed above, merely teach excipients for stabilizing a monoclonal HER2 antibody and therefore does not cure deficiency of Wolff. Thus, Applicants respectfully submit that these references do not render the instant claims obvious.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

5. Claim Rejections 35 USC §112

Claims 8 and 9 are rejected under 35 USC §112, first paragraph for not enabling one of skill in the art to make and use the invention commensurate in scope with the claims. While the Action

acknowledges that the specification is enabled for using the commercial antibodies, UJ127 and 5G3, to inhibit cell proliferation of tumor cells that express L1CAM, the Office Action asserts that the specification does not provide reasonable enablement for making and using any antibody to inhibit any carcinoma. Applicants traverse this rejection.

Applicants respectfully submit that they have amended Claim 8 to clarify the invention and the pending claim now recites, "A pharmaceutical composition for treatment of a tumor cell that expresses L1CAM . . .." Applicants respectfully submit that these amendments address and overcome the asserted basis for the non-enablement rejection, since the claims now are not directed to any carcinoma, but only to those that express the L1CAM protein target of the antibody. The claims are thus commensurate in scope with the specification.

With regards to the assertion made in the Action that the specification lacks enablement for using any L1CAM antibody for treating cancer, Applicants respectfully submit that the two commercially-available L1CAM antibodies used in their specification were merely examples and are not limiting of the entire invention. In addition, references cited on page 10 of the Action to support the Patent Office argument against enablement of use of any L1CAM antibody for treating cancer, on the contrary, support enablement of claims as instantly presented where any unconjugated L1CAM antibody is used for treatment of L1CAM-expressing cancers.

Contrary to the assertions in the Action, the first cited reference, Primiano *et al.* clearly teaches specific growth inhibitory effects of UJ127 and 5G3 antibodies on all cancer cells that express L1CAM on their cell surface (*see* the entire reference, specifically page 47 under the heading "L1CAM-specific antibodies inhibit the growth of different tumor cell lines, but not normal cells").

Similarly, the second cited reference, Arlt *et al.*, teaches growth-inhibitory effects of L1CAM antibodies, L1-11A and chCE7, on tumor cells expressing L1CAM (*see* the entire reference, more specifically on page 937, right column, paragraph 5; page 938, left column, first paragraph; and Table 1). Contrary to the assertions in the Action, both L1CAM antibodies taught in the reference, L1-11A and chCE7, cause growth inhibition of cancer cells expressing L1CAM. The growth inhibition was specific to L1CAM-expressing cancer cells as the antibodies did not cause any growth inhibition of L1CAM-negative cell line (PC3). The antibody, HEA125, shown not to cause growth inhibition in cancers expressing L1CAM in Arlt *et al.* is in fact directed against *Ep-CAM* and not L1CAM (page 937, left column under the heading "Antibodies" and on page 938, left column, paragraph 1). Hence, the fact that a set of L1CAM antibodies that differ from the ones disclosed by Applicants specifically inhibited proliferation of cancer cells expressing L1CAM on their surface (and not L1CAM

negative cell lines) provides strong support for Applicants' claim that any L1CAM antibody can be used for treatment of cancer cells expressing L1CAM.

Therefore, the disclosure of Applicants' specification taken in light of teachings in art, and more specifically Arlt *et al.* and Primiano *et al.*, enables the skilled worker to reasonably expect that any L1CAM unconjugated antibody or fragment thereof can be used for the practice of the methods of the invention for treating any cancer cell expressing L1CAM.

In view of the discussion above, the Applicants therefore request the Examiner to reconsider and withdraw the rejection under 35 USC §112, first paragraph.

Claims 8 and 9 are rejected under 35 USC §112, first paragraph for not enabling one of skill in the art to make and use the invention commensurate in scope with the claims. The Office Action asserts that the specification does not provide reasonable enablement for specific, site-directed accumulation of the anti-L1CAM antibody or binding-fragment thereof to any cancer with the intention of treating cancer. Applicants traverse this rejection.

The Office Action argues that L1CAM antibody or L1CAM binding fragment would have an approximate molecular weight of 250 KD and it would be difficult to deliver such a high molecular weight molecule into some tumors. To support its argument, the Action cites Jain *et al.* (1994) that discusses various impediments in drug delivery. Applicants acknowledge the reference, however they respectfully point out that the reference was published in 1994, and since then the art of drug delivery has made significant advancement. At the time of filing the instant application (October 2003), antibody/drug delivery was a well-established art, as is evident by the disclosure in Applicants' specification in paragraph [0012], where Applicants discuss successful use of a monoclonal antibody (Herceptin®) against Her2/Neu for treatment of breast cancer. In addition, one of the references cited in the Action, Hoefnagel *et al.* (published in 2001) itself provides a method to successfully deliver [^{131}I]-conjugated L1CAM antibodies to xenografts in mice. Furthermore, if Hoefnagel could successfully deliver conjugated antibody having a *higher* molecular weight than unconjugated antibodies as taught by the instant invention, then one of skill in the art can successfully deliver the unconjugated antibodies using similar delivery methods as those taught by Hoefnagel. These examples clearly demonstrate that site-specific delivery of antibodies to cancer was a standard procedure in the art at the time of invention, and therefore respectfully contend that the disclosure is enabling in light of the teachings in the art.

The Action further cites Chatterjee *et al.* (1994) to support the argument that the specification lacks a working example showing that the composition is effective in animals with a pre-existing cancer.

According to MPEP 2164.01, paragraph 3, *"The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation."*

Applicants respectfully submit that the specification discloses *in vitro* experiments that show inhibition of growth of cancer cells expressing L1CAM. Furthermore, the specification teaches (paragraph [0043] through [0048] and [0055]) methods for administering L1CAM antibodies or fragments thereof. Procedures for treating cancer using antibodies is a well-developed art, as set forth above, and Applicants' disclosure provided in the specification is sufficient to enable one of skill in art to successfully practice treatment of L1CAM cancers as claimed. Also, as evidenced by Primiano *et al.* (Cancer Cell, 2003, see page 50, left column, first paragraph: "In fact, most of the cancer chemotherapeutic drugs produce cytostatic inhibition at low doses and cell death at higher doses"), it is well understood in the art that reagents that cause cytotoxic or cytostatic effects on cancer cells *in vitro* are potent cancer drugs. Hence, based on the specification in light of knowledge prevalent in the art, one of skill can expect antibodies against L1CAM to effectively work as anticancer drugs. Further, one of skill can envision and perform experiments to achieve successful treatment of L1CAM-expressing cells as discussed above, all without undue experimentation. According to MPEP 2164.01, paragraph 3, *"The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."* The extent of Applicants' disclosure puts no undue experimentation burden on the skilled worker, who would be able to successfully practice claimed invention.

The Action further cites Gura *et al.* (1997) to support its argument that results from clonogenic assays and mouse xenograft models would not necessarily correlate with results expected in human patients. As discussed above, Applicants respectfully submit that *in vitro* experimentation has become a conventional method to find successful agents for cancer treatment. Therefore, Applicants do not need to explicitly disclose *in vivo* experiments nor results in humans, to ensure that antibodies shown to work *in vitro* can be established to be successful in humans or animals for cancer treatment without undue experimentation. *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2D 1436 (Fed. Cir. 1995).

Based on the arguments presented above, Applicants request the Examiner to reconsider and withdraw the rejection under 35 USC §112, first paragraph.

CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If the Examiner believes it to be helpful, he is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff LLP

Date: February 26, 2007

By: /Kevin E. Noonan/
Kevin E. Noonan, Ph.D.
Reg. No. 35,303